REMARKS

Claims 1, 5, 7-10, 14-18, 22, 24-35, 37-40, and 42-44 remain in the application.

Favorable reconsideration is respectfully requested.

Rejections Under §112, First Paragraph (Written Description and Enablement):

The continuation of this rejection stems, in part, from counsel's misunderstanding of the Examiner's earlier use of the term "RNasin." Specifically, in the Advisory Action dated August 27, 2007, the Office stated that "the specification [is] enabling for the claimed method of use of rat or human RNasin." Undersigned counsel took that to mean that the Office deemed the specification enabling for RNA inhibitor proteins derived from rats and humans. Thus, in Applicants' prior response, Claim 1 was amended to recite that the RNase inhibitor protein "is derived from rats, human placentas, or recombinant human placental sources." In a subsequent conversation with the Examiner (held on September 4, 2007), it was clarified that the in using the term "RNasin," the Examiner was referring to the specific RNasin-brand protein disclosed in the specification.

That issue now having been clarified, Applicants respectfully traverse both the written description and enablement rejection on the basis that they set an improperly elevated standard for purposes of satisfying the written description and enablement requirements of 35 USC §112, first paragraph.

Applicants again note that the claims have been amended throughout to require that the RNase inhibitor protein is "derived from rats, human placentas, or recombinant human placental sources." Applicants thus respectfully traverse the Office's statement at page 5, second paragraph, of the Office Action dated December 10, 2007. Here, in continuing this rejection, the Office States, in relevant part:

> [T]hat the RNase inhibitor protein is 'derived from rats, human placentas, or recombinant human placental sources'... is not, in and of itself, successful in overcoming the current rejection on the basis that applicants' description of a few RNase inhibitor proteins does not describe or enable the scope of the claims drawn to methods of use involving **any and all RNase inhibitor proteins** and a specific combination or heat and buffer conditions.

(Emphasis added.) Applicants traverse this rationale on two grounds: First, the statement is not reflective of the positive language of the claims. The claims do not encompass using "any and all RNase inhibitor proteins." The claims positively require using an RNase inhibitor protein that is "derived from rats, human placentas, or recombinant human placental sources." Thus, not just any RNase inhibitor protein will do the trick. The inhibitor protein must be derived from the specific sources required by the claims.

Second, Applicants do not have to list every single species falling within a generic phrase in order to enable the generic phase. The specification as filed describes at least four (4) distinct types of proteinaceous RNase inhibitors, all of which will work in the present invention, and all of which are derived from humans or rats. Having described several species of RNase inhibitor proteins that fall within the genus now recited in the claims, Applicants respectfully submit that the specification as filed contains sufficient written description and enablement to support the current claims.

Also as noted earlier, defining a generic term by listing a number of exemplary species that fall within the generic term is a an approved approach to defining a generic term. See MPEP §2164.08 and *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, by specific example or broad terminology, is not important." (Emphasis added.)

Thus, in the present application, the specification clearly discloses human-derived RNase inhibitor proteins (both native and recombinant), rat-derived RNase inhibitor proteins, as well as porcine-derived RNase inhibitor proteins (which are no longer recited in the claims). All of these types of proteins, as well as others, are commercially available products. See Exhibits A, B, C, D, E, and F submitted with Applicants' prior response dated November 27, 2006.

Regarding the revised guidelines concerning compliance with the written description requirement, these guidelines are promulgated at MPEP §2163, which state, in relevant part:

> Possession may be shown in a variety of ways including... describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18

> USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "**whatever characteristics sufficiently distinguish it**"). (Emphasis added.)

On this point, it must again be stressed that Applicants **are not** claiming the RNase inhibitor protein itself. Thus, many of the cases cited in MPEP §2163 (such as *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398, (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), are **inapplicable** to the present claims. Applicants are not claiming a composition of matter or a compound, but rather a method. In short, Applicants respectfully submit that the Office is applying a formulaic approach to the written description requirement, when the Guidelines clearly call for a more flexible approach:

> An adequate written description of the invention may be shown by **any** description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483

Applicants therefore respectfully submit the specification provides a reasonable amount of information to convey to a person of ordinary skill in the art that Applicants were in possession of the invention at the time the application was filed. Applicants likewise submit that the specification clearly enables, in a commensurate fashion, the claims as they currently stand.

As noted in the application as filed, and in previous arguments submitted by the Applicants, rat-derived RNase inhibitor proteins and human-derived inhibitor proteins are articles of commerce. Native human placental RNase inhibitor protein and recombinant human placental RNase inhibitor protein are both available commercially. They are well-known, commercial compounds that have been described extensively in both the patent literature and the scientific literature. See the discussion in the application as filed starting at page 11, last paragraph, and extending to page 12, first full paragraph. Because the claims now positively require that the RNase inhibitor protein is "derived from rats, human placentas, or recombinant human placental sources," Applicants respectfully submit that the rejections under §112, first paragraph (written description and enablement) are untenable.

Specifically addressing enablement, it is not seen how the specification fails to enable practicing the positively recited method using any type of protein RNase inhibitor, without limitation. All that is required is for the practitioner to follow the protocol recited in the specification using the chosen RNase

inhibitor protein. There is no uncertainty or ambiguity in how the protocol is to proceed. Applicants therefore submit that the specification enables the full breadth of the claims as they currently stand.

The Office asserts that the Applicants must establish a structure-activity relationship with respect to the RNase inhibitor protein. See page 7 of the Office Action. But no such structure-activity relationship is required to enable the claims to the level required by §112, first paragraph. Applicants are not required to have any knowledge at all about how or why an inventions works. Applicants therefore traverse the enablement rejection as being contrary to both the case law and the MPEP. All that is required to satisfy the enablement requirement is that the disclosure, when filed, contains sufficient information regarding the subject matter of the claims to enable one skilled in the pertinent art to make and use the claimed invention. See MPEP §2164.01. Applicants submit that the specification as filed clearly enables one of ordinary skill in the art to practice the invention using an RNase inhibitor protein "derived from rats, human placentas, or recombinant human placental sources." No knowledge of the structure of the RNase inhibitor protein is required to practice the invention - all that is required is that the protein be an RNase inhibitor protein in the first place. And, as noted in several earlier responses, Applicants need not have any knowledge of how the invention functions in order to satisfy both the written description and enablement requirements of §112, first paragraph.

In light of the above comments, Applicants submit that the continued rejection of the claims under §112, first paragraph, written description and enablement, is untenable. Withdrawal of these two rejections is respectfully requested.

Rejection of Claims 10 and 14-17 Under 35 USC §102(b) Over Ambion, Inc., TechNotes 8(2) "SUPERase.In: The Right Choice for Protecting Your RNA," hereinafter "Ambion":

Applicants respectfully traverse this rejection because Claim 10 positively requires that an RNase inhibitor protein solution be combined with a first solution containing RNA, to yield a mixture. The **mixture** (*i.e.*, the RNA **and** the RNase inhibitor) is then heated to 50°C. This is distinctly different from the experiment described in the Ambion technical literature.

In the Ambion protocol, the test reflected in Fig. 2 was to measure latent RNase activity within the RNase inhibitors themselves. The RNase inhibitors **alone** were heated to 67°C for 15 minutes. At no point, however, was a combination of the RNase inhibitor **and** a RNA template heated to a temperature greater than 37°C. This is clear from both the description of Figure 2 of the Ambion paper and the accompanying text.

The description for Figure 2 of Ambion states, in relevant part:

> To detect latent RNase actvity, the **inhibitors** were incubated at 67°C for 15 minutes under reducing and oxidizing conditions to release any bound contaminating RNases. 200 U of each inhibitor **was then tested with a fluor/quenched RNA substrate** using the RNase Alert® assay. Reactions were monitored in real-time at **37°C** over 60 minutes in 5-minute increments.

This passage indicates that the RNase inhibitors **alone** were heated to 67°C to release any latent RNase activity entrained within the inhibitors themselves. Only after this heating step was an RNA substrate actually added to the mixture. It is only at this point that the reaction mixture in Ambion contains **both** an RNase inhibitor **and** a RNA. At this point the reactions proceeded at 37°C, **not** 67°C. So at no point in this experiment is the combination of a RNase inhibitor **and** a RNA heated above 37°C.

The text of the Ambion paper reflects this same aspect of the experiment: **only** the RNase inhibitor was heated to 67°C. See the second page of Ambion, second-to-last paragraph:

> The data in Figure 2 address whether **pre-heating of RIs** [RNase inhibitors] releases latent RNase activity associated with the inhibitors.... Preheating SUPERase•In, in contrast, caused no detectable release of RNase, as exhibited by the lack of signal fluorescence elevation over background.

Again, it was the inhibitors alone that were heated to 67°C, not the RNase inhibitors plus the RNA substrate. In the Ambion literature, the reaction solution that contained both the RNase inhibitor and the RNA was heated only to 37°C.

The present claims, however, positively require that a mixture containing both RNA and RNase inhibitor be heated to at least 50°C. This was not done in Ambion. Applicants therefore respectfully submit that this rejection is improper. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 5, 7-10, 14-18, 22, 24-29, 31-35, 37-40, and 42-45 Under §103(a) Over Mizutani et al. in View of Ambion:

Applicants respectfully traverse this rejection because there is no technological reason or motivation to combine the two references in the first instance. Therefore the Office has not established a *prima facie* case of obviousness.

Mizutani et al. is directed to a one-step RT-PCR protocol. Thus, the first step involves reverse-transcribing an RNA template to an RNA-DNA hybrid. In Mizutani, this was done by incubating the RNA tempate at 42°C for 60 minutes. See page 550, third full paragraph. At this point in the protocol, **there is no longer a need to protect the RNA**. The RNA target has already been reversed transcribed. If any RNases were present in the reaction cocktail, the reaction cocktail would have to be protected **before** and **during** the reverse-transcription reaction. In Mizutani, that reaction takes place at 42°C.

But once the RNA has been reverse transcribed, the template for amplification is not the template RNA, but the reverse-transcribed complementary DNA, which is subsequently amplified using a *Taq* polymerase. At this point in the process, there is no need to protect the RNA because the RNA has already been transcribed to DNA. Hence, there is no motivation to add a RNase inhibitor protein at this point in Mizutani's reaction. In short, there is no technical reason to add a RNase inhibitor to Mizutani's protocol at the point the reaction temperature is elevated to 95°C to activate the *Taq* polymerase. And at the point where a RNase inhibitor protein would be useful in Mizutani's protocol, the temperature is set at 42°C.

The Mizutani et al. paper is silent with respect to an RNase inhibitor. Mizutani et al. do not use any type of RNase inhibitor. But *if* an RNase inhibitor were used, it would be utilized at only one of two temperatures: Mizutani's 42°C (the temperature at which the RNA reverse-transcription reaction takes place and during which the RNA template must be protected from degradation by RNase activity) or Ambion's 37°C. At no point do the **combined** references teach or suggest that is it beneficial to heat the inhibitor combined with the RNA template to a temperature of no less than 90°C (a positive requirement of Claim 1). On this point, Applicants are not addressing the references

individually, but in combination. The combination of Mizutani et al. and Ambion does not teach or suggest the beneficial aspects of using an RNase inhibitor in combination with a high temperature. And, as a point of indisputable fact, Ambion clearly teaches away from using such a high temperature.

The **combined** references do not suggest heating an RT-PCR reaction solution plus an RNase inhibitor to 90°C *prior* to adding RNA template to the solution because the Ambion paper clearly teaches that such a maneuver **will serve only to release latent RNase activity from the RNase inhibitor**. The released RNase activity would then destroy the RNA template. In other words, the Ambion paper clearly teaches that if there is latent RNase activity associated with RNase inhibitor, heating the inhibitor to 90°C will release that RNase activity (which will then digest the RNA template). Therefore, the combined references strongly discourage such a heating step. The whole goal in RT-PCR is to get the reverse-transcription step completed before the RNA template gets destroyed by the action of RNases. Therefore, anything that might **increase** RNase activity in the reaction cocktail (such as high heat that would release latent RNase activity from the inhibitor) is strongly discouraged.

As noted earlier, in the Ambion protocol, the test reflected in Fig. 2 was to measure latent RNase activity within the RNase inhibitors themselves. The RNase inhibitors **alone** were heated to 67°C for 15 minutes. At no point, however, was a combination of **RNA** and the RNase inhibitor heated to a temperature greater than 37°C. This is clear from both the description of Figure 2 of the Ambion paper and the accompanying text, as noted in the prior section of this response. Again, it was the inhibitors alone that were heated to 67°C, not the RNase inhitors plus the RNA substrate. Ambion does this not as a beneficial temperature at which to run an RT-PCR reaction, or to improve the functionality of the RNase inhibitor itself, but to show that if the inhibitor has latent RNase activity, the heat treatment will (detrimentally) release that pent up RNase activity. This outcome is **undesirable**. Thus, there is no technological motivation to make the combination of Mizutani et al. with Ambion - it is detrimental to the stated utility of the Mizutani et al. protocol. It is well-settled law that where a proposed modification is detrimental to the utility stated in the applied reference, a prima facie case of obviousness has not been shown.

When the two references are combined, the only temperatures that are technologically advantageous according the explicit teaching of both references is either Ambion's 37°C or Mizutani's 42°C. The present claims, however, require a temperature of 90°C.

Applicants therefore submit that this rejection is improper. Withdrawal of the same is respectfully requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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